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# Reprioritisation of Liver Export Protein Synthesis in Patients with Decompensated Alcoholic Liver Disease

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## Abstract

**Background:** Decompensated alcoholic liver disease is associated with abnormalities in protein synthesis. The relationship of this to reprioritisation of hepatic export proteins and markers of the systemic inflammatory response is unclear. We examined the longitudinal relationship between albumin and fibrinogen synthetic rates and disease severity in decompensated alcoholic liver cirrhosis.

**Patients and Methods:** Hepatic protein synthetic rates were measured in patients with decompensated Childs grade B or C alcohol-related cirrhosis using a validated technique, based on incorporation of deuterated phenylalanine into the plasma pool of albumin and fibrinogen. As a measure of liver export protein reprioritisation, we calculated the fibrinogen and albumin synthetic rates and the Acute Phase Protein Quotient (APPQ; the ratio of these rates). Serum CRP and fibrin D-Dimer were recorded. Measurements were at baseline and on clinical recovery at 4-6 weeks.

**Results:** 17 patients were studied. All patients had hypoalbuminaemia with elevated median C-reactive protein (CRP), D-dimer, bilirubin and prothrombin times. Median albumin and fibrinogen synthetic rates were reduced resulting in marginally increased APPQ. On follow up (n=10), there was reduction in Child-Pugh score ($p<0.01$), plasma concentrations of Fibrin D-dimer ($p<0.01$), CRP ($p<0.01$), bilirubin ($p<0.01$) and prothrombin time ($p<0.01$). Plasma albumin concentrations increased ($p<0.01$) and synthetic rates of both albumin ($p<0.05$) and fibrinogen ($p<0.10$) increased marginally such that median APPQ remained similar.

**Conclusion:** Patients with decompensated alcohol-related cirrhosis had low albumin and fibrinogen synthetic rates and raised CRP indicative of systemic inflammation. On recovery, albumin synthetic rate increased and CRP levels fell, although albumin and fibrinogen synthetic rates remained below normal. Further studies assessing the interaction between protein synthesis and systemic inflammation in chronic liver disease are indicated.

**Keywords:** Alcoholic liver disease; Albumin; Fibrinogen; Protein synthesis; Systemic inflammation

## Introduction

Patients with decompensated chronic liver disease often require prolonged hospitalisation, during which time supportive management is undertaken and specific therapies given with the aim of a gradual improvement in liver function. Alcohol excess is an important cause of liver cirrhosis and accounts for a significant proportion of hospital admissions with this disease [1-3]. Liver cirrhosis is associated with abnormalities in liver protein synthesis [4-7], a feature shared with other disease states such as cancer [8-10].

Normal liver protein synthesis can be divided into that of fixed and export proteins, and in total accounts for 15% to 25% of total body protein synthesis [11,12]. The fixed hepatic proteins that include structural cytoplasmic and mitochondrial proteins account for approximately 50% of hepatic protein synthesis in normal subjects with export protein synthesis accounting for the other 50% [11,13].

Of the export component, albumin synthesis (approximately 80%) and fibrinogen synthesis (approximately 10%) are quantitatively the most important [14,15]. These proteins play a key role in the systemic inflammatory response, with albumin recognised as a negative acute phase reactant and fibrinogen a positive acute phase reactant [16,17]. Previous work in cancer patients with an acute-phase response suggests that the changes in plasma concentrations of these proteins in certain disease states are due to reprioritisation of liver export protein synthesis [4,16,18].

The low serum albumin characteristic of decompensated cirrhosis is a strong prognostic indicator and is a parameter of the Child-Pugh Scoring (CPS) system for assessing disease severity [19]. The hypoalbuminaemia seen in cirrhosis has been reported to be associated with a defective immune response, poor nutritional status and adverse outcome [20]. Previously, it has been assumed that this low serum albumin was due to reduced synthesis. However, studies in hypoalbuminaemic cancer patients have reported an increased albumin fractional synthetic rate [9,14,16].

Fibrinogen is a substrate in the coagulation cascade and patients with decompensated liver cirrhosis are known to exhibit complex coagulation and fibrinolytic abnormalities [10,21]. Studies in patients with cancer and chronic heart failure show that fibrinogen synthesis is preserved or increased as part of the acute phase response [15,22,23]. To date, there are limited data on albumin and fibrinogen synthesis rates in patients with decompensated alcohol related liver cirrhosis.

The aim of the present study was to examine the longitudinal relationship between disease severity, total albumin and fibrinogen synthetic rates and C-reactive protein (CRP; as a marker of systemic inflammation) in patients with decompensated alcohol related liver disease during a period of hospitalisation and out-patient follow-up.

## Patients and methods

### Study design and sample

Patients with Childs grade B or C alcohol related cirrhosis were recruited following hospital admission with worsening ascites or jaundice. Cirrhosis was confirmed by standard clinical and laboratory data and imaging. No patient had evidence of GI bleeding or sepsis, with all patients having negative blood and urine cultures, and no evidence of bacterial peritonitis on diagnostic ascitic tap.

Routine measurement of haematological and biochemical parameters, recording of clinical parameters and measurement of albumin and fibrinogen synthetic rates were undertaken at baseline.

Out-patient follow-up measurement of these synthetic rates was planned 4-6 weeks after the baseline measurements upon recovery from the acute episode of decompensation. The study was approved by the local Ethics Committee and informed consent was obtained in all patients.

### Study protocol

The present study used the rate of appearance of a known quantity of deuterium labelled phenylalanine into circulating plasma albumin and fibrinogen to estimate their respective hepatic synthetic rates.

Albumin and fibrinogen fractional synthetic rates were measured using a validated phenylalanine flooding dose technique previously described in detail [12,24-28]. Briefly, patients were asked to attend the department after an overnight fast and an intravenous cannula was placed into each antecubital fossa vein.

A solution containing 3500 mg of L-phenylalanine mixed with 350 mg [$^2H_5$]L-phenylalanine or 350 mg [$^2H_8$]L-phenyalanine in 0.5% saline made up to 200 ml was then infused rapidly through a 0.2 μm filter over 10 min through one of the cannulae.

The solution was prepared under sterile conditions, tested for sterility and absence of pyrogens. Blood samples were drawn at 10, 20, 40, 60, 80, 120 min after the start of the infusion into EDTA tubes from the contralateral arm, spun down in a cooled centrifuge at 4°C for 15 min, and stored at -80°C. As tracer will reside in the protein pool for weeks [15], each subject received one of the two phenylalanine isotopomers at baseline with the other at follow-up.

### Sample preparation

The methods for the assessment of hepatic protein synthesis using deuterated phenylalanine have been described elsewhere [26], but briefly the rate of fibrinogen synthesis was reflected by the incorporation of labelled phenylalanine into the plasma pool of fibrinogen. For free phenylalanine analysis, 1 ml plasma samples were diluted with 1 ml of deionised water.

Diluted samples were then deproteinised by ultrafiltration (30000 molecular weight cut-off Centrifree cone, Amicon, Gloucestershire, UK) and acidified, and the amino acids were purified by cation exchange. [$^2H_5$]-phenylalanine enrichment was measured by gas chromatography-mass spectrometry (GC-MS) as its ethoxycarbonyltrifluoroethyl ester derivative [27]. This derivative was chosen as it gives good precision for [$^2H_5$]-phenylalanine analysis while giving equivalent and improved precision for [$^2H_{8]}$-phenylalanine analysis [28].

The fractional synthetic rate (FSR) was calculated by dividing the rate of change of the appropriate phenylanine isotopomer enrichment of albumin or fibrinogen by the area under the curve of precursor enrichment versus time. The FSR corresponds to the percentage of the intravascular albumin mass (IAM) synthesised per day (%/day). The absolute or total synthetic rate (TSR) was calculated as the FSR × IAM (plasma concentration × plasma volume) in mg/kg/day.

We have previously carried out simultaneous direct measurements of albumin and fibrinogen TSR in normal fasted subjects [12]. From these data, we derived the Acute Phase Protein Quotient (APPQ) which is the ratio of the total synthetic rate (TSR) of fibrinogen/albumin. This ratio is independent of plasma volume changes and should be a sensitive measure of liver export protein reprioritisation. In normal fasted subjects, normal median APPQ was measured at 0.14 (0.10-0.25).

### Statistical analysis

Data are presented as median and range. Where appropriate, data were tested for statistical significance using the Mann-Whitney U test, and comparison of paired data was carried out using the Wilcoxon signed rank test. Differences were considered significant when the chance of their occurrence by sampling error was <1 in 20 ($p<0.05$). All statistical analyses were performed in SPSS Version 18.0 (SPSS Inc).

## Results

17 patients with decompensated alcohol related cirrhosis were recruited to the study, with baseline characteristics shown in Table 1. Median age was 50 years and the majority (n=15) of participants were male. Three patients had been abstinent from alcohol for four weeks or longer prior to admission.

Twelve patients fulfilled the common clinical criteria for alcoholic hepatitis (alcohol excess within 4 weeks of admission, serum bilirubin >80 μmol/l, AST and ALT <500 and absence of other causes of liver disease), with ten having a modified discriminant function (mDF)>32 and two having a Glasgow alcoholic hepatitis score (GAHS) ≥ 9.

Sixteen patients had Childs grade C cirrhosis and one patient had Childs grade B cirrhosis. Clinically detectable ascites was present in sixteen of the seventeen patients. All patients had hypoalbuminaemia and evidence of decompensated alcohol related liver cirrhosis with evidence of a systemic inflammatory response as inferred by CRP above the normal range. No patients had evidence of bacterial sepsis as evidenced by negative blood, urine and ascitic fluid culture.

All patients had median fibrin D-dimer, bilirubin and prothrombin time above the normal range, but median fibrinogen was within the normal range. With reference to total protein synthetic rates, the median rates of both albumin and fibrinogen were below the normal range such that their ratio (APPQ) was marginally elevated compared with controls.

| | Reference range | Patients (n=17) |
|---|---|---|
| Age (years) | N/A | 50 (38-68) |
| Sex (M:F) | N/A | 15:2 |
| BMI | 20-25 | 26.8 (18.2-36.6) |
| Plasma volume (ml) | 2700-3000 | 3154 (2189-3738) |
| Albumin (g/L) | 35-56 | 25 (20-31) |
| Fibrinogen (g/l) | 1.5-4.0 | 2.9 (1.8-4.6) |
| Fibrin D-dimer (ng/ml) | 70-499 | 937 (384-1018) |
| C-reactive protein (mg/l) | <10 | 31 (7-94) |
| Bilirubin (µmol) | <20 | 147 (40-679) |
| Prothrombin time (secs) | 9-12 | 22 (18-30) |
| Ascites (no/yes) | N/A | 16 / 17 |
| Child-Pugh score | 5-15 | 12 (9-13) |
| Albumin TSR (mg/kg/day) | 208 (122-287) | 48 (29-126) |
| Fibrinogen TSR (mg/kg/day) | 28 (23-55) | 11 (15-28) |
| APPQ Median (range) | 0.14 (0.10-0.25) | 0.17 (0.10-0.67) |
| TSR=Total Synthetic Rate<br>APPQ=Acute Phase Protein Quotient | | |

**Table 1:** Admission characteristics of patients with decompensated liver cirrhosis.

There was the suggestion of a negative correlation between baseline CPS and albumin TSR although this did not reach statistical significance (correlation coefficient -0.405, p=0.107). No correlation was seen between baseline CPS and fibrinogen TSR (p=0.370), or between either albumin or fibrinogen TSR and C-reactive protein (p=0.844, p=0.978). There was no significant difference between the sub-group with clinical alcoholic hepatitis and the other patients with regard to albumin TSR (p=0.230), fibrinogen TSR (p=0.492) or APPQ (p=1.00), although the C-reactive protein was slightly higher in the alcoholic hepatitis group (p=0.08).

10 of the 17 patients attended for follow-up measurements. The baseline and follow-up data of these patients are shown in Table 2. On follow-up there was a significant clinical improvement as evidenced by an improvement of CPS (p<0.01). There were also reductions in plasma concentrations of Fibrin D-dimer (p<0.01), CRP (p<0.01), bilirubin (p<0.01) and prothrombin time (p<0.01) and an increase in plasma albumin (p<0.01). The total synthetic rates of both albumin (p<0.05) and fibrinogen (p<0.10) increased marginally, such that the median APPQ remained similar. Of the seven who failed to attend for follow-up measurement, none had died within the 6 week follow-up period after assessment of medical notes and discussion with their general practitioner. We understand all seven had returned to drinking alcohol to excess.

| | Admission (n=10) | Recovery (n=10) | p-value |
|---|---|---|---|
| Plasma volume (ml) | 3154 (2273-3738) | 3123 (2218-3706) | 0.017 |
| Albumin (g/L) | 25 (22-31) | 32 (22-35) | 0.007 |
| Fibrinogen (g/l) | 3.0 (1.8-4.6) | 2.7 (1.6-4.2) | 0.515 |
| Fibrin D-dimer (ng/ml) | 957 (864-1018) | 878 (313-922) | 0.008 |
| C-reactive protein (mg/l) | 27 (7-94) | 8 (6-23) | 0.005 |
| Bilirubin (µmol) | 143 (49-490) | 61 (15-83) | 0.005 |
| Prothrombin time (secs) | 22 (18-29) | 19 (14-26) | 0.007 |
| Child-Pugh score | 12 (9-13) | 9 (6-13) | 0.007 |
| Albumin TSR (mg/kg/day) | 61 (36-126) | 96 (73-189) | 0.011 |
| Fibrinogen TSR (mg/kg/day) | 15 (5-28) | 23 (12-38) | 0.093 |
| APPQ Median (range) | 0.17 (0.10-0.67) | 0.22 (0.12-0.42) | 1.000 |
| TSR=Total Synthetic Rate<br>APPQ=Acute Phase Protein Quotient | | | |

**Table 2:** Admission and recovery characteristics of patients with decompensated liver cirrhosis.

## Discussion

The results of the present study show that, compared with normal ranges, patients admitted with decompensated alcohol related liver cirrhosis had a reduction in both their albumin and fibrinogen total synthetic rates by 70% and 45% respectively. This was in the context of a systemic inflammatory response as indicated by raised CRP. On follow-up, both albumin and fibrinogen total synthetic rates increased but remained significantly below the normal range (particularly the albumin synthetic rate) in the context of a fall in both CRP and CPS. The relative contributions of albumin and fibrinogen to export protein synthesis remained similar. These longitudinal results suggest that in addition to improved liver function, the systemic inflammatory response may play a role in determining liver protein export synthesis.

It is of interest that the relationship between the acute phase response and adverse outcome has become recognised in non-cirrhotic disease states. Systemic-inflammation based scores, such as the modified Glasgow Prognostic Score, have been shown to provide accurate prognostic information in cancer patients independent of tumour site [29,30]. Several studies have shown an association between the acute phase response and adverse outcome across a range of cancer types [29-31]. This association is also seen in other disease states such as end-stage heart failure [22] and acute liver failure [32].

With reference to outcome in liver cirrhosis, Cazzaniga and coworkers have reported that the systemic inflammatory response syndrome (SIRS) is closely related to severity of liver disease in cirrhotic patients as evidenced in the relationship with serum bilirubin, INR and the Model for End-Stage Liver Disease (MELD) score [33]. In their study, SIRS also predicted the development of portal hypertension-related complications and was closely correlated with in-hospital death. Shawcross and colleagues have suggested that

the mediators of SIRS, including nitric oxide and pro-inflammatory cytokines, may exacerbate the neuropsychological effects of the hyperammonaemia seen in cirrhotic patients and may contribute to progression of hepatic encephalopathy [34]. Also, Thabut and coworkers reported that the presence of SIRS (with or without infection) was an independent prognostic factor in patients with cirrhosis and acute renal failure [35]. Whether moderation of the systemic inflammatory response by anti-inflammatory drugs or other means may improve outcome is unclear.

The value of CRP as a surrogate marker of SIRS and predictor of outcome in cirrhosis has been a topic of increasing interest. Bota and colleagues reported no significant difference in serum levels of acute phase proteins between cirrhotic and non-cirrhotic critically ill intensive care patients [36]. However Cervoni reported that in patients with decompensated cirrhosis (with or without infection), persistently elevated CRP concentration predicted short-term mortality independent of MELD score, and was superior to the clinically-assessed SIRS [37]. Also, Papp et al. [38] reported that CRP was a reliable marker of bacterial infection in patients with cirrhosis, although its accuracy decreased in advanced cirrhosis or in the presence of ascites.

The limitations of our study include the fact that the diagnosis of cirrhosis was based on clinical and laboratory data, without recourse to liver biopsy. However this is standard practice in many centers due to the complications of percutaneous biopsy, limited availability of transjugular biopsy and debatable impact on management in this patient group. We also did not measure formal SIRS scores, as not all the required clinical parameters were recorded for all participants. Our study numbers were also small and only 10 of the 17 recruited patients attended for their follow-up study. All of the seven who failed to attend for follow-up had been drinking heavily until their initial admission, and we understand they had all started drinking again after discharge. Additionally, we performed our follow up analysis after a recovery period of 4-6 weeks, and while it was assumed that this time period was sufficient to allow full recovery to baseline liver function, it may be that a longer time interval would have seen a greater change in protein synthetic rates. To our knowledge, this is the only longitudinal study measuring hepatic export protein synthesis in decompensated alcohol-related cirrhotic patients with evidence of systemic inflammation. Follow up study with a larger patient group over a longer period of follow up would be of value.

In conclusion, these results add to the growing body of evidence concerning the important role of systemic inflammation in alcohol-related liver cirrhosis and its relationship with liver function. It is possible that moderation of the systemic inflammatory response is a potential therapeutic target for improving liver function in patients with decompensated alcoholic cirrhosis.

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